Remarks

Claims 21-40 are pending in the present Application. Of these claims, claims 31-40 have been withdrawn from consideration as a result of an earlier restriction requirement. Applicants previously (in response filed January 25, 2006) canceled claims 31-40 as non-elected claims, while at the same time preserving the right to file one or more divisional application on the invention of the cancelled claims, if Applicants choose to do so.

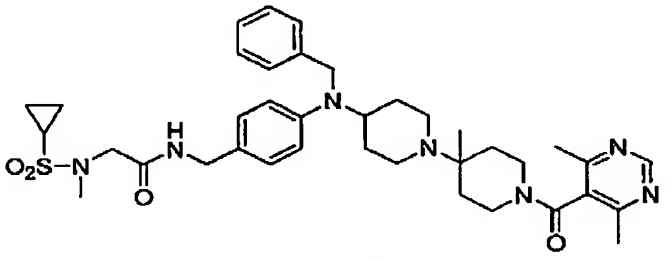
In the present paper, Applicants have amended claims 21-24 (claims 25-30 are dependent on the amended claims) to exclude subject matter outside the scope of the restriction requirement, i.e., subject matter that does not correspond to R^1 being MR^4 wherein M is phenyl, R^2 is nonheterocyclic, R^3 is substituted or unsubstituted pyrimidine or pyrimidine N-Oxide, and R^4 is $-(C_1-C_6)$alkyl-$N(R^{21})SO_2R^{22}$.

Obviousness-type Double Patenting Rejection

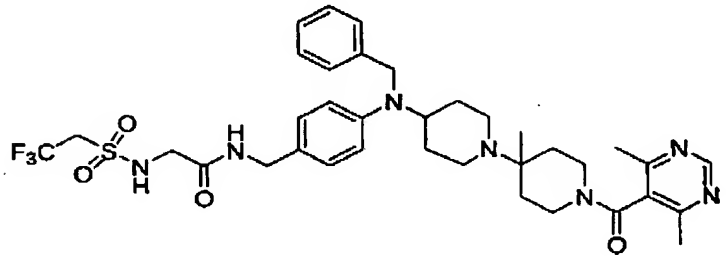
The Examiner has maintained her provisional rejected claim 24 and the scope of claims 21-23, 25-30 wherein R^1 is MR^4 wherein M is phenyl, R^4 is $-C_{1-6}$Alkyl-$NR^{21}SO_2R^{22}$, R^2 is non-heterocyclic, and R^3 is substituted or unsubstituted pyrimidine, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 10/979,075, in view Tetrahedron, Vol. 42, No. 21, pp. 6039-6045, 1986, authors Rubini et al. (hereinafter "Rubini et al."). Applicants again respectfully disagree with the Examiner and traverse this rejection for the same reasons as set forth in the previous response with further arguments below.

The Examiner asserts that the copending claims are drawn to analogous compounds of the instantly "elected" scope of R^4, i.e., $R^4 = C_{1-6}$Alkyl-$NR^{21}SO_2R^{22}$. She also asserts that the difference between the instant elected scope and the copending species is that instead of R^4 being C_{1-6}Alkyl-$NR^{21}SO_2R^{22}$, the copending claims are drawn to compounds wherein an ethylene chain of the C_{1-6}Alkyl linker of the R^4 is replaced by an amide bond.

The Examiner referred especially to claim 17, 1st and 6th compounds on page 70 of copending Application Serial No. 10/979,075 (equivalent to US Patent Application Publication US2006/0025441 (published February 2, 2006). The 1st and 6th compounds on page 70 of the copending application correspond to the 2nd and 7th compounds respectively on page 43 of US2006/0025441. These two structures are set forth below and have been labeled Structure A and Structure B respectively:



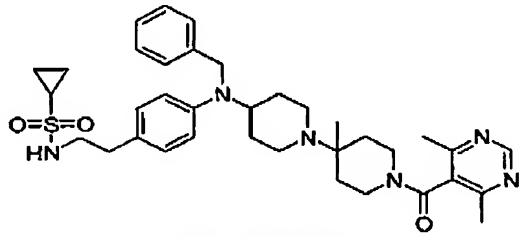
Structure A



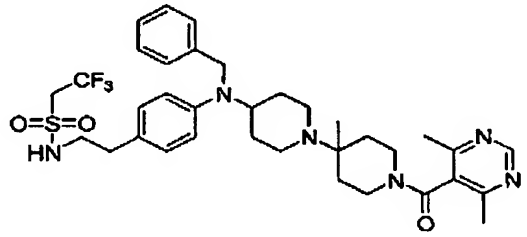
Structure B

The Examiner asserted that the ethylene linker and an amide bond are considered amide bond surrogate units and refers to Rubini et al., especially page 6039, 9th line from bottom. She further asserted that one having ordinary skill in the art in possession of the copending claims would be motivated to replace the amide bond of the linkage with an amide bond surrogate, i.e., an ethylene chain which would be the instant claims. She asserts that the modification of two sets of compounds with conventional skill in biologically active compounds with amide bond surrogate is prima facie obvious because one would expect such modification to produce more compounds with analogous activity.

In essence then the Examiner is asserting that Structures A and B above of the copending application would respectively render Stuctures C (third compound of present claim 24) and D (fourth compound of present claim 24) set forth below obvious in view of Rubini et al.:



Structure C



Structure D

Applicants again respectfully submit that the Examiner has failed to establish a prima facie case of obviousness in the present rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

It is respectfully submitted that there is no motivation in Rubini et al. alone or in combination with the copending application to render obvious the presently claimed invention.

Rubini et al. addresses the problem of serious limitations associated with developing **peptides** as potential therapeutic agents owing to their rapid metabolism and poor transport properties. It suggests overcoming these limitations by creating non-peptide counterparts which would **interact similarly with a common receptor** inducing identical physiological and pharmacological effects. Rubini et al. discloses that the replacement of the amide bonds in the peptide backbone with amide bond surrogates is an important tool toward the transformation of a peptide toward a non-peptidic peptidomimetic compound, and lists several isosteric modifications as amide bond surrogates, such as ψ [CH_2-S], ψ [NH-CO], ψ [CH_2-CH_2], ψ [CH_2-NH], ψ [CO-CH_2], ψ [(E) or (Z) CH=CH]. Rubini et al. discloses that one goal of these modifications is to **achieve maximal topographical equivalence with the trans-amide bond**, and that a close approximation in geometrical terms has been obtained with the ψ [(E) CH=CH] isosteric modification (Rubini et al., page 6039; emphasis added).

The difference between structures A and B of the copending application and structures C and D of the present invention is that the –CH_2C(=O)NHCH_2- molety of structures A and B is replaced with –CH_2CH_2- in structures C and D of the present invention. This modification is nowhere suggested in Rubini et al.

The present compounds are not peptides or pseudopeptides as in Rubini et al., but are nonpetidic small molecules. Furthermore Rubini et al., provides no motivation to one of ordinary skill in the art to modify a –CH_2C(=O)NHCH_2- moiety into a –CH_2CH_2- molety to arrive at the presently claimed compounds.

It is clear from the disclosure in Rubini et al. that isosteric modification of amide bonds in peptides with amide bond surrogates such as an ethylene group are only feasible in cases where there are similar intermolecular interactions which make the non-peptide analogs interact similarly with a common receptor as the peptides. Such interactions would not be expected to be similar for nonpeptidic small molecules that have undergone isosteric modification. Were this not so, then any amide bond in any small molecule could be replaced with an ethylene group, a position that defies complete

chemical logic. Yet, this is precisely what the Examiner appears to be asserting. According to the Examiner's logic, an amide bond would be chemically equivalent to an ethylene bond in all chemical compounds. This simply is not and cannot be true. Rubini et al. says nothing about isosteric modification of functionalities in nonpeptidic small molecules. Applicants have also carefully considered the Patani article on Bioisoterism (*Chem. Rev.* 1996, 96, 3147-3176) referred to by the Examiner, and find no support therein for the Examiner's assertion. The Patani article is no more relevant than Rubini et al., and at best can be considered cumulative. It simply points out that "peptide bonds and peptide fragments have been replaced with a wide variety of structural moieties in attempts to convert peptides into chemically stable and orally available molecules". (Patani, page 3170).

Applicants contend Rubini et al. only establishes that bioisosteric replacement of the amide functionality is only applicable in certain specialized situations in peptide chemistry due to considerations of steric and intermolecular interactions. Applicants do not find any support in Rubini et al., for the blanket proposition that an amide functionality in any small molecule can be replaced with an ethylene group or for the modification of a $-CH_2C(=O)NHCH_2-$ moiety into a $-CH_2CH_2-$ moiety.

It is respectfully submitted that Rubini et al. or Patani et al. provides no motivation for transforming the compounds of the copending application, which are not peptides, through isosteric modification of the amide group into ethylene group to arrive at the presently claimed compounds. Such a motivation is not only lacking through explicit language in Rubini but it is also lacking through express suggestion, or knowledge of those skilled in the art. Simply put, one of ordinary skill in the art would not, given the teaching in Rubini et al. or Patani et al., be motivated to modify Structure A into Structure C and Structure B into Structure D as set forth above. The driving forces for bioisosteric replacements for the amide in peptides are those that result in similar intermolecular interactions and topographical equivalence. These driving forces are not expected to be the same for the present non-peptide small molecules. One of ordinary skill in the art will clearly recognize the differences between the two.

The Examiner is respectfully requested to withdraw the present rejection for the reasons set forth above,

CONCLUSION

Applicants respectfully request prompt reconsideration of present claims 21-30, and an early allowance of the application.

If the Examiner wishes to comment or discuss any aspect of this application or response, applicants' undersigned attorney invites the Examiner to call him at the telephone number provided below.

September 15, 2006
Schering-Plough Corporation
2000 Galloping Hill Road
Patent Department, K-6-1, 1990
Kenilworth, NJ 07033
Tel: (908) 298-2198
Fax: (908) 298-5388

Respectfully submitted,

Krishna G. Banerjee

Krishna G. Banerjee, Ph.D.
Attorney for Applicants
Reg. No. 43,317